Serious Adverse Event Reporting

Study AC-060A202: CONTROL

Miyuki Tomioka

ACTELION

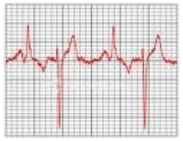
Global Drug Safety Goals

- To ensure the safety of the patients
- To detect trends and signals concerning the safety of Actelion drugs
- To comply with safety reporting requirements worldwide

What is an Adverse Event (AE)?

- **Any adverse change from the patient's baseline condition, regardless of the relation to the study drug.**

- **An AE includes**
  - Disease or condition detected after baseline
  - Exacerbation of pre-existing disease
  - Increase in frequency or intensity of pre-existing disease or condition
  - Clinically significant abnormal test (ECG, lab test…) that was not abnormal at baseline or worsened
  - Events that occur as a result of protocol-mandated procedures



Serious Adverse Event

An SAE is defined as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
  - Event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had occurred in a more severe form
- Hospitalization: admission of hospital or prolongation of existing hospitalization as a result of an AE
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly / Birth defect
- Medically significant or requiring intervention to prevent one of the other outcomes listed above

Important medical events may be considered as SAEs if, based upon appropriate medical judgment, they may jeopardize the patient and/or require medical intervention to prevent one of the outcomes listed above.

Reporting AEs/SAEs from Clinical Trials

Investigator

Adverse Event

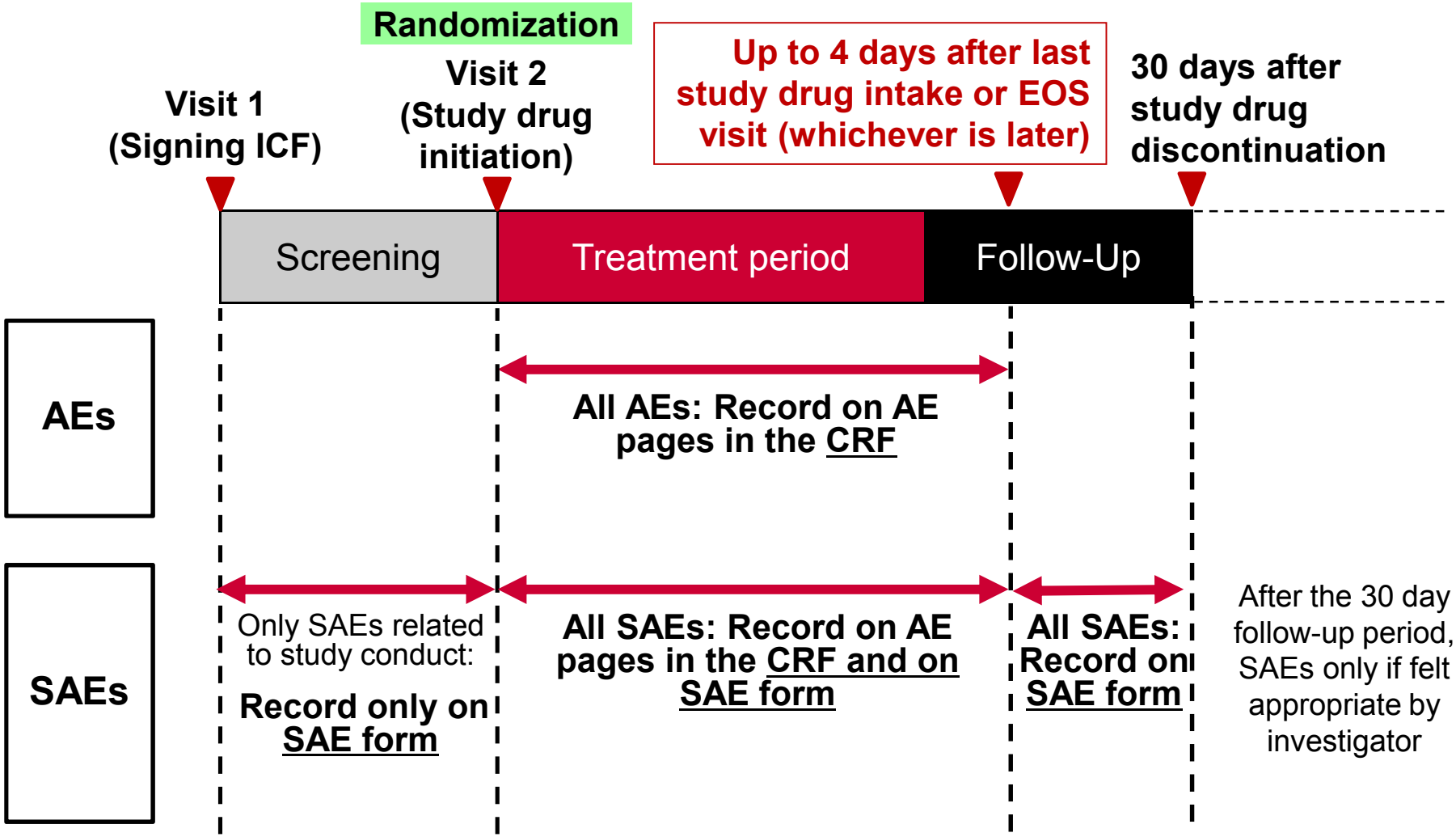
Complete AE page in CRF

Serious Adverse Event

Complete SAE form

Within 24 hours of knowledge

AE/SAE Reporting throughout the study



AE/SAE Follow-up

- AEs still ongoing 4 days after treatment must be followed up until:
  - Thirty days after stopping study drug
  - Resolution
  - Stabilization

  OR
  - The event is otherwise explained

- SAEs still ongoing at the EOS visit must be followed up until:
  - Resolution
  - Stabilization

  OR
  - The event is otherwise explained

Seriousness vs. severity

Seriousness

Non-serious
or
Serious

Severity

Mild, moderate or
severe in intensity

- A mild, moderate or severe AE may or may not be serious.
  - A severe event is not necessarily serious, and a serious event may not be severe; e.g.,
    - Nausea lasting several hours may be rated as severe, but may not be clinically serious
    - Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day
- Seriousness (rather than severity) serves as a guide for defining regulatory reporting obligations

Causality/relationship assessment

- A relationship to the study drug has to be assessed in each AE by the investigator, based on the investigator's judgment and knowledge of the AE:
  - **Related (= "Yes"):** Reasonably related to the use of the study drug
  - **Not related (= "No"):** Not reasonably related to the use of the study drug

Relationship matters for reporting purposes!

The causality assessment is important for subject to reporting to Health Authorities, EC/IRBs and Investigators worldwide

Would you report?

- A road traffic accident?
- A fall?
- A surgery?

Is this a Serious Adverse Event?

REMEMBER

When in doubt ...

SEND IT OUT !!!

What is a SUSAR?

- **S**uspected **U**nexpected **S**erious **A**dverse **R**eaction
  - Suspected: reasonably related to study drug
  - Unexpected: not documented in the current Investigator's Brochure
  - Serious: ICH definition (Protocol §4.3)

Definitions of Unexpected adverse events

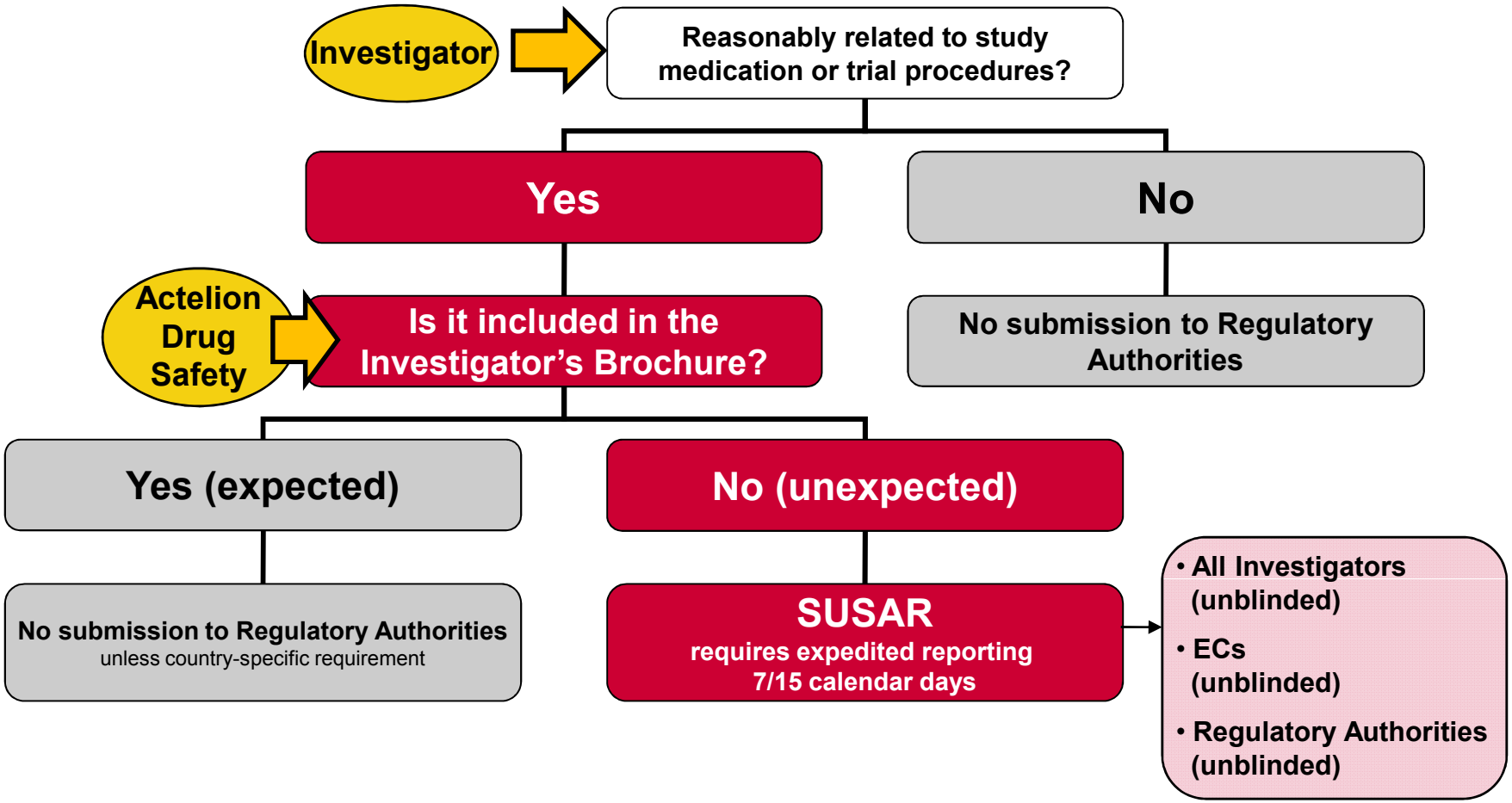
- Any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator Brochure (IB) (more specific, more severe or an increase in the rate of occurrence)

- "Unexpected" refers to an adverse drug experience that has not been previously observed (e.g., in the IB) rather than from the anticipation based on the pharmacological properties of a medicinal product.

FDA 21 CFR (Code of Federal Regulations Title 21) **312.32(a)**

ICH E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting)

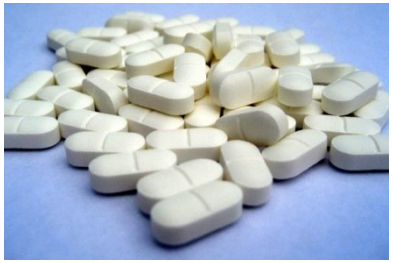
Serious Adverse Events (SAEs) in Clinical Trials



SUSAR notification responsibilities

SUSAR submission to:	By:
Regulatory Authorities	Actelion
Investigators	Actelion
Data Monitoring Committee	Actelion
Ethics Committees / Institutional Review Boards	Actelion **OR** **Investigator** e.g. Hungary, Israel, Serbia, Ukraine, USA **In this situation it is the responsibility of the investigator to inform the EC/IRB and to ensure that submissions are done within the required timelines as per national regulations**

Unblinding



Investigator

*"The emergency unblinding of single cases by **investigators** in the course of a clinical trial should only be performed if **relevant for the safety** of the trial subject"*

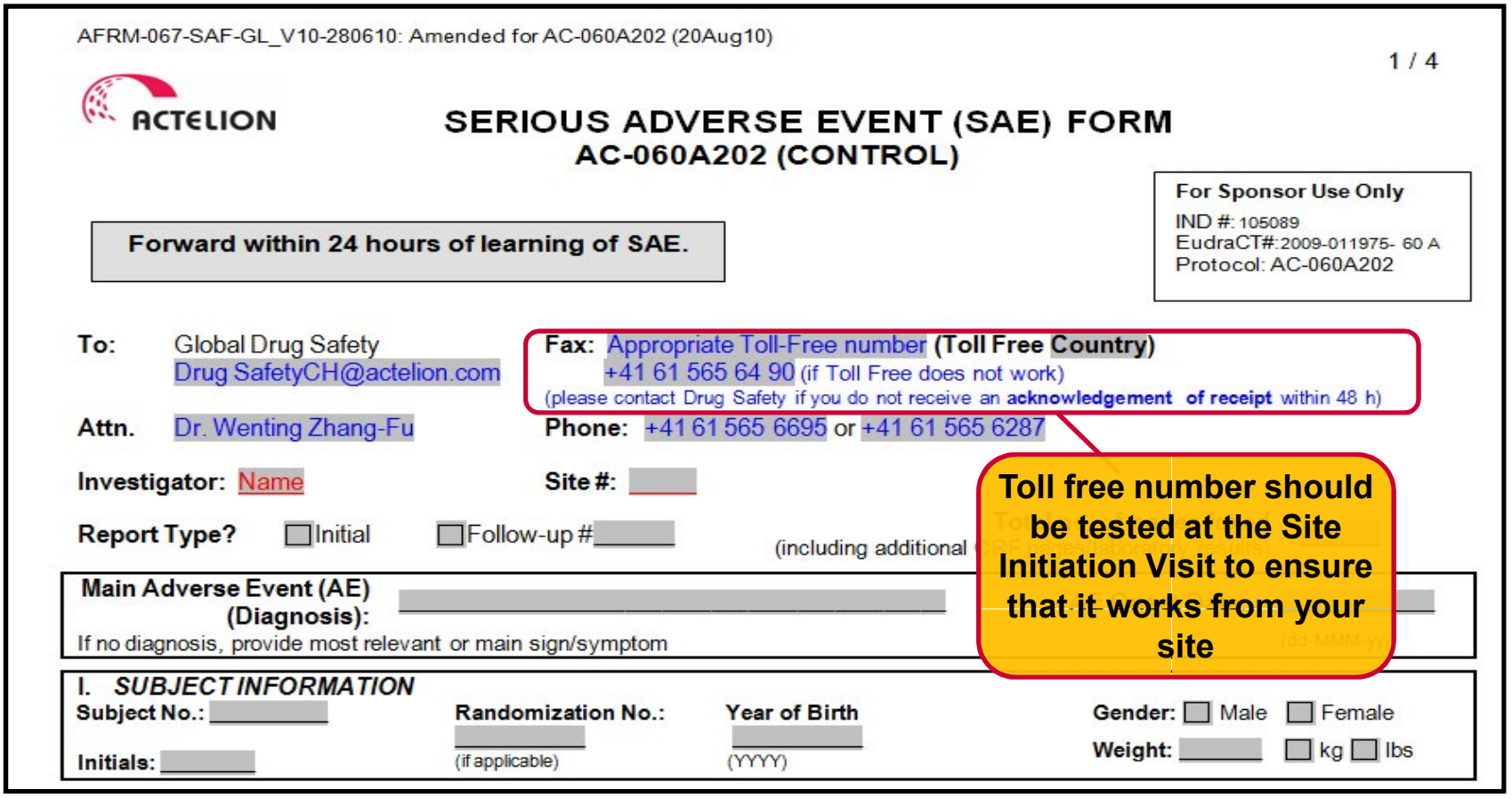
→ before unblinding, **every attempt should be made** by the investigator to discuss the intended code break with Actelion

Actelion

SUSARs will be unblinded in Actelion Global Drug Safety (GDS) prior to submission to Health Authorities, ECs/IRBs and Investigators

Serious Adverse Event Form (1)

Drug Safety will send acknowledgment within 2 working days with unique MCN



AFRM-067-SAF-GL_V10-280610: Amended for AC-060A202 (20Aug10)

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ACTELION

SERIOUS ADVERSE EVENT (SAE) FORM
AC-060A202 (CONTROL)

For Sponsor Use Only
IND #: 105089
EudraCT#:2009-011975- 60 A
Protocol: AC-060A202

Forward within 24 hours of learning of SAE.

To: Global Drug Safety
Drug SafetyCH@actelion.com

Fax: Appropriate Toll-Free number **(Toll Free Country)**
+41 61 565 64 90 (if Toll Free does not work)
(please contact Drug Safety if you do not receive an **acknowledgement of receipt** within 48 h)

Attn. Dr. Wenting Zhang-Fu

Phone: +41 61 565 6695 or +41 61 565 6287

Investigator: Name

Site #:

Report Type? ☐ Initial ☐ Follow-up #

(including additional

Main Adverse Event (AE) (Diagnosis):
If no diagnosis, provide most relevant or main sign/symptom

I. *SUBJECT INFORMATION*

Subject No.:

Initials:

Randomization No.:
(if applicable)

Year of Birth
(YYYY)

Gender: ☐ Male ☐ Female

Weight: ☐ kg ☐ lbs

Toll free number should be tested at the Site Initiation Visit to ensure that it works from your site

Note: MCN: Manufacturer Control Number

Dear Dr. Investigator,

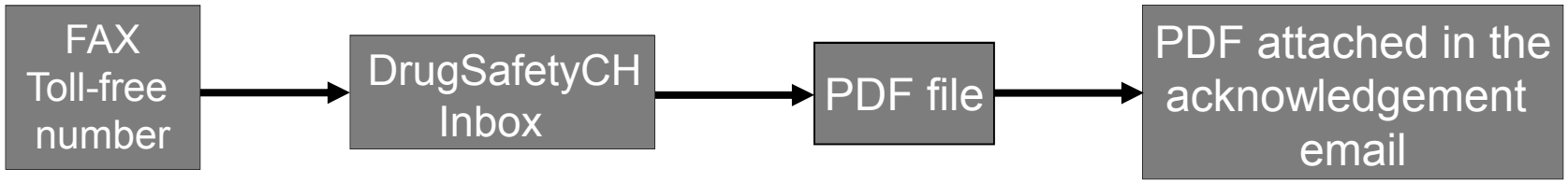
This is to acknowledge that we have received initial information regarding:

Patient No.: **0011-00011**
Study No.:
Event:
Onset Date: **DD-MMM-YY**
MCN Number: **A-CH2009-12345** → Manufacturer Control Number

Please do not hesitate to call us should you have any queries regarding the above.
Thank you for sending us this information.

Kind regards

Drug Safety Administrative Assistant



Serious Adverse Event Form (2)

IV. *ADVERSE EVENT INFORMATION*

Record Adverse Event (diagnosis/syndrome) as on Page 1, and complete this entire Section IV.
*If more than one SAE has occurred, fill out an additional Section IV per SAE and attach to this report **.*

Adverse Event (Diagnosis)

If no diagnosis, provide most relevant or main sign/symptom _____

AE Onset Date (dd-MMM-yy) _____ AE Onset Time	RELATIONSHIP Is there a reasonable possibility that the event was related to the use of the study drug? ☐ Yes ☐ No	MAXIMUM INTENSITY *See protocol for definitions*	ACTION TAKEN WITH STUDY DRUG As a result of the event	OUTCOME Tick only one	SERIOUSNESS Please tick all that apply:
Onset of first symptoms, not when event became serious		☐ Mild	☐ None	☐ Resolved without sequelae	☐ Death
Date (or death date if outcome is death) _____	*If no, do you consider the event to be related to protocol-mandated procedures, tick if yes* ☐	☐ Moderate	☐ Dose reduced	☐ Resolved with sequelae	☐ Life-Threatening
		☐ Severe	☐ Dose increased	☐ Not resolved	☐ Disability
		☐ Not Applicable	☐ Temporarily interrupted	☐ Death	☐ Congenital Anomaly
			☐ Permanently discontinued	☐ Unknown / Lost to follow-up	☐ New Hospitalization
			☐ Not applicable		☐ Prolongation of Hospitalization
					☐ Medically significant
					☐ Intervention Required to prevent one of the above

Did the Adverse Event abate after stopping, interrupting, or reducing the dose of the study drug?
☐ Yes ☐ No ☐ Not applicable

Abate = improve or resolve

Did the Adverse Event reoccur after reintroducing the study drug? ☐ Yes ☐ No ☐ Not applicable

Serious Adverse Event Form (3)

Hospitalization Details *(Complete if Hospitalization is ticked above)*	Death Details *(Complete if Death is ticked above)*
Admission Date (dd-MMM-yy)* _____ Discharge Date (dd-MMM-yy) _____ ** i.e. first day of hospitalization*	Date of Death (dd-MMM-yy) _____ **Autopsy performed?** ☐ Yes ☐ No **Autopsy results attached?** ☐ Yes ☐ No **Primary Cause of Death:** _____

Provide autopsy report if available

Do not forget to mask patient name on all documents

Serious Adverse Event Form (4)

VIII. *REPORTER INFORMATION*

Investigator Name: _____ Institution: _____

Address: _____ Country: _____

Email address: _____

Name and Position of person completing this form: Phone #: _____

_____ Fax #: _____

Email address: _____

Did you also send a form to country's regulatory authority? ☐ Yes ☐ No

Date you became aware of this SAE *(initial report only)*: _____

Investigator or Study Physician Signature: Date: _____ (dd-MMM-yy)

Medical Terminology

- When completing the AE page or SAE form, medical terminology should be used for the diagnosis, or to describe the signs/symptoms.

- Abbreviations should be avoided as they can mean different things:

e.g., ARF → Acute Renal Failure
→ Acute Respiratory Failure
→ Acute Rheumatic Fever

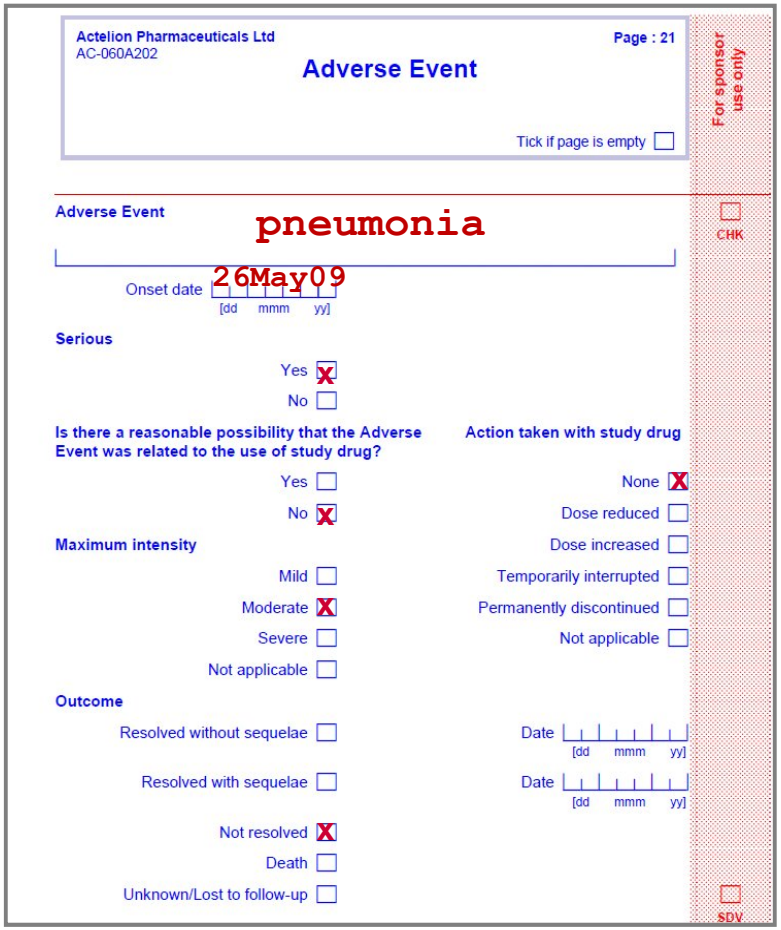
Source documents

- **Source documents:** e.g., hospital notes and discharge summaries.

- Please do not send detailed supplementary source documents on a routine basis unless specifically requested by Actelion or considered relevant to the reported SAE
  - *An example of relevant case: if an autopsy report is available, this should be sent to Actelion with the SAE form*

- Information from supplementary source documents relevant to the reported SAE should be summarized and entered on the SAE form.

AE CRF Page vs. SAE form



Actelion Pharmaceuticals Ltd
AC-060A202

Page : 21

Adverse Event

Tick if page is empty ☐

For sponsor use only

☐ CHK

Adverse Event

pneumonia

Onset date 26May09 [dd mmm yy]

Serious

Yes ☒
No ☐

Is there a reasonable possibility that the Adverse Event was related to the use of study drug?

Yes ☐
No ☒

Action taken with study drug

None ☒
Dose reduced ☐
Dose increased ☐
Temporarily interrupted ☐
Permanently discontinued ☐
Not applicable ☐

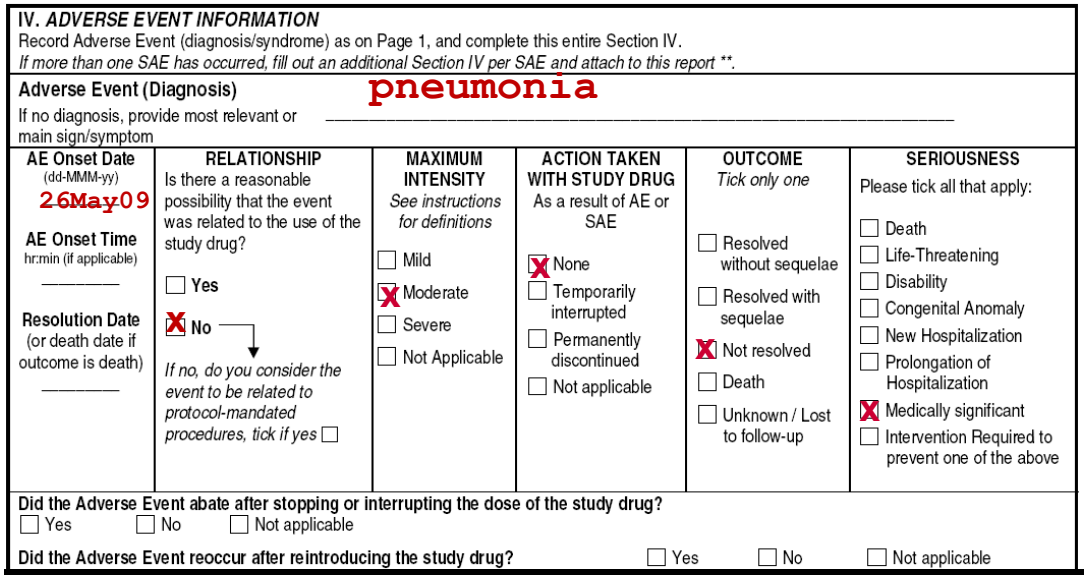
Maximum intensity

Mild ☐
Moderate ☒
Severe ☐
Not applicable ☐

Outcome

Resolved without sequelae ☐ Date [dd mmm yy]
Resolved with sequelae ☐ Date [dd mmm yy]
Not resolved ☒
Death ☐
Unknown/Lost to follow-up ☐

☐ SDV



IV. *ADVERSE EVENT INFORMATION*

Record Adverse Event (diagnosis/syndrome) as on Page 1, and complete this entire Section IV.
*If more than one SAE has occurred, fill out an additional Section IV per SAE and attach to this report **.*

Adverse Event (Diagnosis)
If no diagnosis, provide most relevant or main sign/symptom: pneumonia

AE Onset Date (dd-MMM-yy)	RELATIONSHIP	MAXIMUM INTENSITY	ACTION TAKEN WITH STUDY DRUG	OUTCOME	SERIOUSNESS
26May09 **AE Onset Time** hr:min (if applicable) ____ **Resolution Date** (or death date if outcome is death) ____	Is there a reasonable possibility that the event was related to the use of the study drug? ☐ Yes ☒ No *If no, do you consider the event to be related to protocol-mandated procedures, tick if yes* ☐	*See instructions for definitions* ☐ Mild ☒ Moderate ☐ Severe ☐ Not Applicable	As a result of AE or SAE ☒ None ☐ Temporarily interrupted ☐ Permanently discontinued ☐ Not applicable	*Tick only one* ☐ Resolved without sequelae ☐ Resolved with sequelae ☒ Not resolved ☐ Death ☐ Unknown / Lost to follow-up	Please tick all that apply: ☐ Death ☐ Life-Threatening ☐ Disability ☐ Congenital Anomaly ☐ New Hospitalization ☐ Prolongation of Hospitalization ☒ Medically significant ☐ Intervention Required to prevent one of the above

Did the Adverse Event abate after stopping or interrupting the dose of the study drug? ☐ Yes ☐ No ☐ Not applicable

Did the Adverse Event reoccur after reintroducing the study drug? ☐ Yes ☐ No ☐ Not applicable

Information on AE page = SAE form

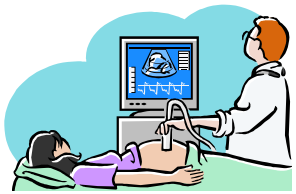
➔less queries sent to site when we perform reconciliation between the clinical database and the safety database

Data Clarification Form (DCF)

- Your opinion of relationship (causality) of each event to study drug or to study conduct
- Site number, Patient (number, gender, age at the time of event)
- Start and stop date and time for suspect medication
- Onset date of event
- Action taken with study drug
- Outcome of the event
- Contact phone or fax number

If answers to the DCF are not received by Drug Safety you will be sent an automatic reminder

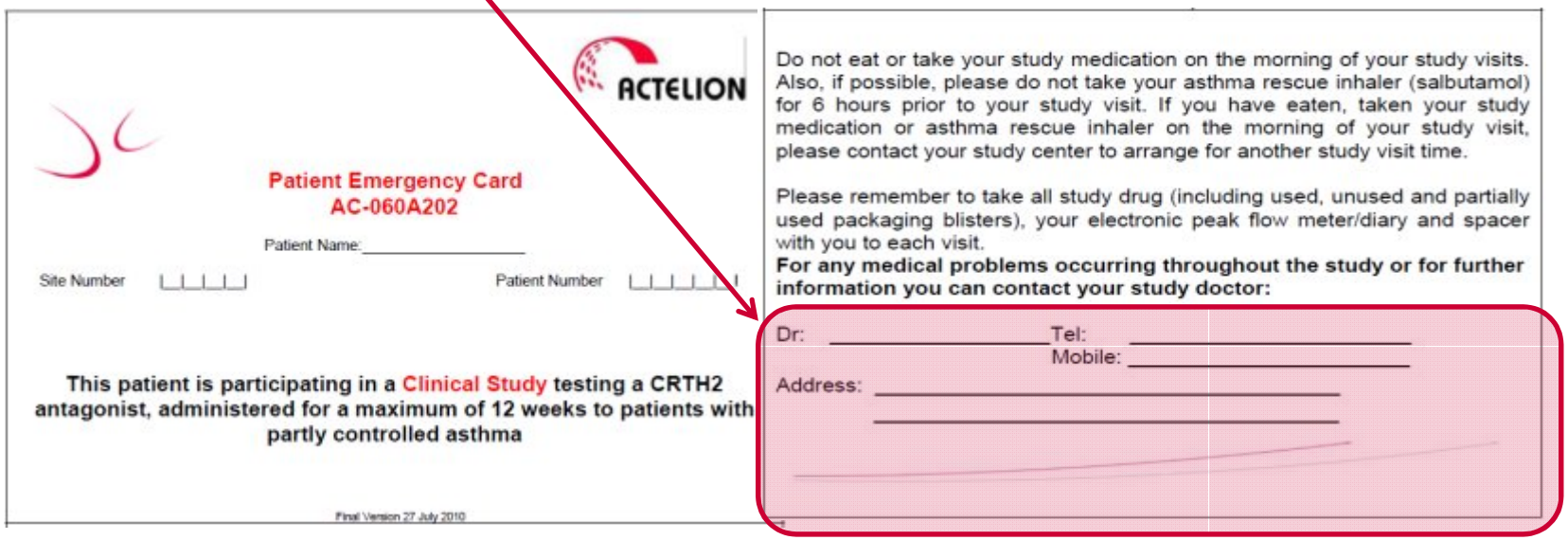
Pregnancy reporting to Actelion



- Any pregnancy occuring during the trial and up to 1 month after study drug discontinuation must be reported to Actelion on a pregnancy form within 24 hours of your knowledge
- Any event during pregnancy that meets the definition of serious must also be reported on a SAE form
- Actelion follows all pregnancies prospectively therefore all outcomes (including normal) must be reported to Actelion. Actelion considers all abortions as medically significant and therefore serious.
- Furthermore, please report to Actelion any medically relevant information regarding the mother, embryo/fetus or newborn as follow-up

Patient's contact for medical issues

- Each Patient will receive a patient card containing the contact details for their treating physician, providing them with 24 hour access to a phyisician if needed.



ACTELION

Patient Emergency Card
AC-060A202

Patient Name:_____

Site Number |_|_|_|_| Patient Number |_|_|_|_|

This patient is participating in a Clinical Study testing a CRTH2 antagonist, administered for a maximum of 12 weeks to patients with partly controlled asthma

Final Version 27 July 2010

Do not eat or take your study medication on the morning of your study visits. Also, if possible, please do not take your asthma rescue inhaler (salbutamol) for 6 hours prior to your study visit. If you have eaten, taken your study medication or asthma rescue inhaler on the morning of your study visit, please contact your study center to arrange for another study visit time.

Please remember to take all study drug (including used, unused and partially used packaging blisters), your electronic peak flow meter/diary and spacer with you to each visit.

For any medical problems occurring throughout the study or for further information you can contact your study doctor:

Dr: _____ Tel: _____

Mobile: _____

Address: _____

_____

Investigator's contact for medical safety questions

Medical issues relating to an **SAE**:

- Jan Vaclavek, Drug Safety Physician

  Tel: +41 61 565 6261 or +41 79 602 7880

  Fax: +41 61 565 6490

- Cecile Valette, Head of Medical Safety Surveillance

  Tel: +41 61 565 6535 or +41 79 784 73 83

Administrative Assistant, Tel: +41 61 565 66 95

For safety reporting, use the fax number pre-printed on the safety forms

Any questions